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Dear Linda,

This letter is a follow-up on our conversation of 9/15/95. As I explained, our results from transfecting growth hormone plasmids into the pancreas *in vivo* via the pancreatic duct led me to the conclusion, that we could successfully use the same simple approach for transfecting foreign DNA into any segment of the gut. I originally conceived of this idea on 9/8/95 and discussed it with Ira Goldfine and Steve Rothman on 9/13/95. The advantages of this approach for gene therapy are tremendous. Using timed release formulations, the genes of interest, along with the vehicle, could be taken by mouth or by rectal suppository.

The gut has several other advantages in addition ease of delivery. The gut epithelial cells (the cells that line the gut) are secretory cells and secrete into the lumen, lymph system and blood stream. Scattered throughout the length of the gut are highly efficient endocrine cells, making the gut the largest endocrine organ in the body. These cells could also be targets for gene therapy, thereby inducing efficient and selective secretion into the blood stream.

The gut is also the largest organ in the immune system. Patches of immune cells are found along the gut and appear to be involved in inducing tolerance to oral antigens (so that we do not develop an immune response to the foods that we eat). This property has recently been used for treating auto-immune diseases such as Type I diabetes mellitus and rheumatoid arthritis, by feeding patients the antigens that are targets for the immune system in these diseases. Giving proteins orally is difficult, of course, since they are usually broken down prior to reaching the immune cells in the gut. By getting the cells of the gut to produce these proteins themselves, long term tolerance and amelioration of the autoimmune disorder could result. The proteins could potentially be targeted to either the epithelial cells lining the gut, the immune cells, or both. The epithelial cells that line the gut may not need to secrete these proteins in order to induce tolerance since these cells continually slough off the villi into the gut lumen, break down, and release their proteins into the gut.

I just wanted to give you a general idea of the invention and its potential uses. I think it is the simplest and potentially most useful formulation of the gene therapy concept so far. I will retain a copy of this letter in my files. I have also included a copy of the results from our recent pancreas transfection experiments.

Sincerely,

Michael S. German, M.D.